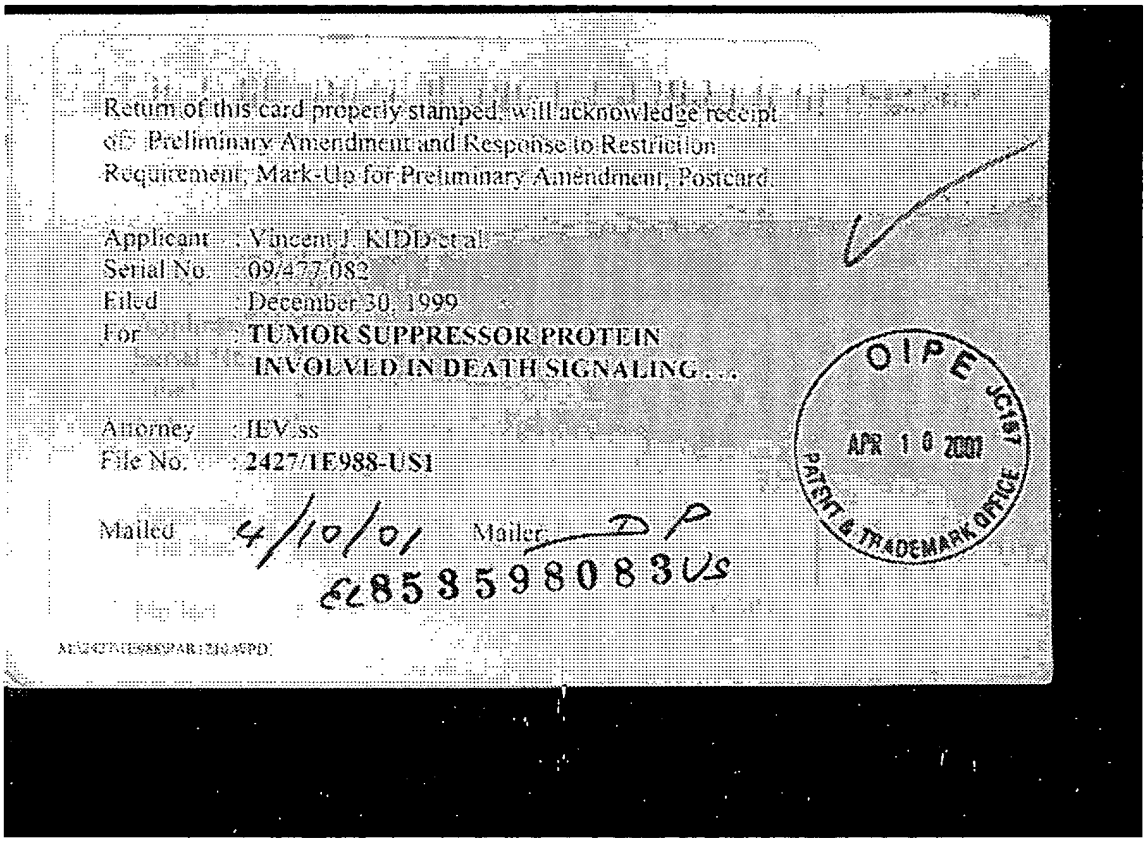

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Applicant : Vincent J. KIDD et al.
Serial No. : 09/477,082
Filed : December 30, 1999
For : TUMOR SUPPRESSOR PROTEIN INVOLVED IN DEATH SIGNALING . . .

Attorney : IEV/ss
File No. : 2427/1E988-US1

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2427/1E988-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Vincent J. KIDD et al.

Serial No.:	09/477,082	Group Art Unit:	1642
Filed:	December 30, 1999	Examiner:	Jennifer Hunt

For: TUMOR SUPPRESSOR PROTEIN INVOLVED IN DEATH SIGNALING, AND DIAGNOSTICS, THERAPEUTICS, AND SCREENING BASED ON THIS PROTEIN

PRELIMINARY AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

In response to the Restriction Requirement mailed March 14, 2001, and in accordance with Rules 142 and 143 of the Rules of Practice, please consider the following election, amendment, and remarks.

AMENDMENT

IN THE CLAIMS:

Please amend claims 21 and 38 pursuant to 37 C.F.R. §1.121 as follows (*see* the accompanying "marked up" version pursuant to 1.121):

1. (Unchanged) A method for detecting inactivation of a *CASP8* gene, comprising detecting a modification of genomic DNA comprising the *CASP8* gene, wherein such a modification results in inactivation of a *CASP8* gene.

2. (Unchanged) The method according to claim 1, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is detected by detecting the absence of a CASP8 protein in a sample from a cell.

3. (Unchanged) The method according to claim 2, wherein the absence of a CASP8 protein is detected by a method selected from the group consisting of immunoassay and biochemical assay.

4. (Unchanged) The method according to claim 1, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is methylation of *CASP8* promoter.

5. (Unchanged) The method according to claim 4, wherein methylation of the *CASP8* promoter is detected by methylation polymerase chain reaction (PCR) assay.

6. (Unchanged) The method according to claim 1, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is a mutation in the *CASP8* genomic gene.

7. (Unchanged) The method according to claim 6, wherein the mutation is selected from the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

8. (Unchanged) The method according to claim 6, wherein the mutation is a deletion in the *CASP8* gene.

9. (Unchanged) The method according to claim 8, wherein deletion of the *CASP8* gene is detected with a labeled nucleic acid probe.

10. (Unchanged) A method for diagnosis or prognosis of a cancer comprising detecting inactivation of a *CASP8* gene, wherein inactivation of the *CASP8* gene is indicative of the presence of a cancer or a poor prognosis.

11. (Unchanged) The method according to claim 10, wherein the cancer is a tumor in which a *myc* gene is amplified.

12. (Unchanged) The method according to claim 10, wherein the cancer is a neuroblastoma.

13. (Unchanged) The method according to claim 10, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is detected by detecting the absence of a CASP8 protein in a sample from a cell.

14. (Unchanged) The method according to claim 13, wherein the absence of a CASP8 protein is detected by a method selected from the group consisting of immunoassay and biochemical assay.

15. (Unchanged) The method according to claim 10, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is methylation of *CASP8* promoter.

16. (Unchanged) The method according to claim 15, wherein methylation of the *CASP8* promoter is detected by methylation polymerase chain reaction (PCR) assay.

17. (Unchanged) The method according to claim 10, wherein the modification of genomic DNA resulting in inactivation of a *CASP8* gene is a mutation in the *CASP8* genomic gene.

18. (Unchanged) The method according to claim 17, wherein the mutation is selected from the group consisting of an insertion in the gene, a deletion of the gene, a truncation of the gene, a nonsense mutation, a frameshift mutation, a splice-site mutation, and a missense mutation.

19. (Unchanged) The method according to claim 17, wherein the mutation is a deletion in the *CASP8* gene.

20. (Unchanged) The method according to claim 19, wherein deletion of the *CASP8* gene is detected with a labeled nucleic acid probe.

21. (Amended) A nucleic acid comprising at least a part of the genomic gene encoding CASP8, wherein the nucleic acid is selected from the group consisting of:

a) a *CASP8* genomic DNA;

b) a *CASP8* promoter;

c) a nucleic acid amplified by primers that correspond to a sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13,

14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, and 28;

d) a *CASP8* exon;

e) a *CASP8* intron;

f) a nucleic acid having at least 15 bases and hybridizable under stringent conditions to a *CASP8* non-coding sequence.

22. (Unchanged) The nucleic acid according to claim 21 which is a *CASP8* genomic DNA having a nucleic acid sequence as depicted in SEQ ID NO: 3, 4, 5, 6, 7, 8, 9, or 10.

23. (Unchanged) The nucleic acid according to claim 21 which is a *CASP8* promoter having a nucleic acid sequence as depicted in SEQ ID NO: 1 or 2.

24. (Unchanged) The nucleic acid according to claim 21 which is an oligonucleotide that hybridizes to the *CASP8* promoter, wherein the oligonucleotide is a PCR primer for the promoter.

25. (Unchanged) The nucleic acid according to claim 21 which is an oligonucleotide having at least 15 bases and hybridizable under stringent conditions to a *CASP8* non-coding

sequence, which oligonucleotide is labeled.

26. (Unchanged) A kit for detecting inactivation of a *CASP8* gene comprising a detection assay for inactivation of a *CASP8* gene.

27. (Unchanged) The kit of claim 26, wherein the detection assay is an immunoassay.

28. (Unchanged) The kit of claim 26, wherein the detection assay comprises oligonucleotide PCR primers for amplification of at least a part of *CASP8* genomic DNA.

29. (Unchanged) The kit of claim 26, wherein the detection assay comprises a labeled oligonucleotide of at least 15 bases that specifically hybridizes to *CASP8* genomic DNA.

30. (Unchanged) A method of treating a cancer in a subject comprising administering an amount of a vector that expresses a gene encoding functional CASP8 effective to express a functional level of CASP8 into cells of the subject.

31. (Unchanged) The method according to claim 30, wherein the cancer is a tumor in which a *myc* gene is amplified.

32. (Unchanged) The method according to claim 30, wherein the cancer is a neuroblastoma.

33. (Unchanged) The method according to claim 30, wherein a *CASP8* gene is inactivated in tumor cells of the cancer.

34. (Unchanged) The method according to claim 30, wherein the vector comprises a promoter that provides for high level expression operatively associated with the gene encoding a functional CASP8, whereby the functional CASP8 is expressed at high levels.

35. (Unchanged) The method according to claim 30, wherein the vector is selected from the group consisting of a defective herpes virus (HSV) vector, a defective adenovirus vector, and a non-viral vector.

36. (Unchanged) A vector that expresses a gene encoding functional human CASP8

in human target cells.

37. (Unchanged) The vector of claim 36 comprising a promoter that provides for high level expression operatively associated with the gene encoding a functional CASP8, whereby the functional CASP8 is expressed at high levels.

38. (Amended) A pharmaceutical composition for treating a cancer comprising the vector of claim 36 and a pharmaceutically acceptable carrier.

39. (Unchanged) A method of screening for a candidate compound that induces death-receptor-mediated apoptosis in cells where a *CASP8* gene is inactivated, comprising contacting cells in which a *CASP8* gene is inactivated with a candidate compound and detecting whether the cell undergoes apoptosis.

40. (Unchanged) The method according to claim 39, wherein the cell comprises a genetically modified death receptor of the Fas/TNFR receptor family operably associated with a reporter gene, whereby activation of the death receptor results in expression of the reporter gene.

41. (Unchanged) The method according to claim 40, wherein the death receptor is DR3.

42. (Unchanged) The method according to claim 40, wherein the reporter gene is a green fluorescent protein (GFP).

43. (Unchanged) The method according to claim 39, wherein inactivation of the *CASP8* gene results from methylation of *CASP8* promoter.

44. (Unchanged) The method according to claim 39, wherein inactivation of the *CASP8* gene results from a mutation in the *CASP8* genomic gene.

45. (Unchanged) A kit for screening for a candidate compound that induces death-receptor-mediated apoptosis in cells where a *CASP8* gene is inactivated, comprising cells in which a *CASP8* gene is inactivated and a detection assay for whether the cell undergoes apoptosis.

46. (Unchanged) The kit of claim 45, wherein inactivation of the *CASP8* gene results from methylation of *CASP8* promoter.

47. (Unchanged) The kit of claim 45, wherein inactivation of the *CASP8* gene results from a mutation in the *CASP8* genomic gene.

REMARKS

Applicants have carefully studied the Office Action mailed March 14, 2001, which issued in connection with the above-identified application. The present response is intended to be fully responsive to all points raised by the Examiner. Favorable reconsideration and an early action on the merits is respectfully requested.

Claims 1-47 are pending and at issue in this application. Claim 21 has been amended to delete an erroneous recitation of SEQ ID NO: 12, which is not a nucleic acid sequence but a peptide sequence corresponding to the substrate specificity determinant of the CASP8 small subunit (*see* page 45, lanes 14-17). In addition, claim 38 has been amended to correct a minor typographical error. Specifically, in the application as filed, claim 38 recited the "vector of claim 32". However, claim 32 is directed to a method of treating cancer and not to a vector. It is claim 36 that is directed to a vector that expresses a gene encoding functional human CASP8 in human target cells. Accordingly, claim 38 has been amended to recite the vector of claim 36. No new subject matter has been added as a result of the above-mentioned amendments.

Restriction Requirement

In the Office Action, the Examiner has required restriction to one of the following Groups of claims under 35 U.S.C. § 121:

Group I: Claims 1-9 and 26-29, drawn to methods of detecting inactivation of *CASP*8 gene and corresponding kits (class 435, subclass 6);

Group II: Claims 10-20, drawn to a method of diagnosis or prognosis of cancer (class 435, subclass 64);

Group III: Claims 21-25 and 36-37, drawn to a nucleic acid sequence and corresponding expression vector (class 536, subclass 23.1 and class 435, subclass 320.1);

Group IV: Claims 30-35, drawn to a method of treating cancer using gene therapy (class 514, subclass 44);

Group V: Claim 38, drawn to a pharmaceutical composition (class 514, subclass 44);

Group VI: Claims 39-47, drawn to a method of screening for a candidate compound and a corresponding kit (class 435, subclass 7.1).

In the Office Action, the Examiner contends that the inventions are distinct because allegedly (i) each method (recited in the claims of Groups I, II, IV, and VI) has different steps and different outcomes; (ii) the products recited in the claims of Groups III and V have different structural features and biological functions, and (iii) the product of Group V can be used to generate polypeptide *in vitro*, which is a materially different process of use compared to the process recited in the claims of Group IV.

In order to be fully responsive to the Requirement for Restriction, applicants hereby elect, with traverse, to prosecute the claims of Group I (claims 1-9 and 26-29) directed to methods of detecting inactivation of *CASP*8 gene and corresponding kits.

Although applicants are making the above election to be fully responsive to the Requirement for Restriction, applicants respectfully traverse the Requirement and reserve the right

to petition therefrom under 37 C.F.R. § 1.144. In particular, applicants respectfully request reconsideration of the Restriction Requirement to allow prosecution of all pending claims in the same application, or, in the alternative, modification of the Requirement to allow prosecution of more than one of the above groups, for the reasons provided as follows.

Under 35 U.S.C. § 121, "two or more independent and distinct inventions . . . in one application may . . . be restricted to one of the inventions". Inventions are "independent" if there is no distinct relationship between the two or more subjects disclosed" (MPEP 802.01). The term "distinct" means that "two or more subjects as disclosed are related . . . but are capable of separate manufacture, use or sale as claimed, AND ARE PATENTABLE (novel and unobvious) OVER EACH OTHER" (MPEP 802.01, July 1988) (emphasis in original). However, even with patentably distinct inventions, restriction is not required unless one of the following reasons appear (MPEP 808.02):

1. Separate classification;

2. Separate status in the art; or,

3. Different field of the search.

Moreover, according to Patent Office examining procedures, "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions" (MPEP 803) (emphasis added).

Applicants respectfully submit that the Groups I-VI fail to define inventions that

warrant separate examination and search. Indeed, claims of Groups I , II, III, and VI are classified in the same search class (class 435) and claims of Groups IV and V are classified not only in the same class (class 514) but also in the same subclass (subclass 44). Accordingly, searches of these groups will be coextensive. In addition, as provided below, the claims in Groups I-VI contain a number of unifying features.

Thus, methods recited in the claims of Groups I, II, and VI are based on detecting the inactivation of *CASP*8 gene (compare, *e.g.*, claims 2, 3, 5, and 9 of Group I with claims 13, 14, 16, and 20 of Group II or with claims 43 and 44 of Group VI). In fact, claims of Group II represent the application of the same method as recited in the claims of Group I to the diagnosis and prognosis of cancer.

Furthermore, the nucleic acid molecules recited in the claims of Group III can be used as hybridization probes or PCR primers to detect the inactivation of *CASP*8 gene according to the methods of Groups I, II, and VI (*see, e.g.*, claims 24 and 25 directed to *CASP*8 promoter-specific PCR primers and labeled *CASP*8-specific hybridization probes, respectively). Indeed, as recited in claims 28 and 29 (Group I), a kit for detecting inactivation of *CASP*8 gene comprises PCR primers and hybridization probes recited in claims 24 and 25 (Group III).

In addition, the CASP8 expression vectors recited in claims 36 and 37 (Group III) can be used in the gene therapy method recited in the claims of Group IV as well as in the pharmaceutical composition recited in claim 38 (Group V). In fact, claim 38 as amended refers back to claim 36 and therefore shares patentability issues with this claim.

In light of the foregoing arguments, it can be concluded that the claims of provisionally elected Group I contain multiple unifying features with the claims of Groups II-VI, and, in particular, with the nucleic acid claims of Group III and diagnostic method claims of Group II. Hence, it is believed that a single search of the features of the methods recited in the claims of Group I would necessarily and unescapably require a search of the subject matter of claims of Groups II and III, and will overlap with the search of the subject matter of Groups IV-VI.

The applicants are aware that, if, based on the arguments presented above, the Examiner decides to modify the Restriction Requirement to consider the nucleic acid claims of Group III together with the method claims of Group I, the Examiner may request election of a single species of nucleic acid sequences from SEQ ID NOS: 1-10 and 12-28 accompanied by a statement of what type of sequence (*i.e.*, intron, exon, promoter, etc.) the species is generic to[1]. In order to be fully responsive to such potential Requirement, applicants hereby elect, with traverse, the *CASP*8 promoter sequence SEQ ID NO: 2.

Although applicants are making the above election to be fully responsive to a potential Restriction/Election Requirement, applicants respectfully traverse the Requirement and reserve the right to petition therefrom under 37 C.F.R. § 1.144. In particular, applicants respectfully submit that the Restriction/Election Requirement is not proper because SEQ ID NOS: 1-10 and 13[2]-

[1] This Restriction/Election Requirement is stated at page 4 of the present Office Action.

[2] As follows from the foregoing amendment and accompanying remarks, SEQ ID NO: 12 is a peptide sequence (*see* page 45, lanes 14-17), which should not be grouped with nucleic acid sequences and was recited in claim 21 in error.

28 represent large (SEQ ID NOS: 1-10) or small (SEQ ID NOS: 13-28) fragments of the same continuous *CASP8* genomic sequence, and have been provided separately exclusively for convenience (*see, e.g.*, page 10, lanes 3-11 and Table 1 at page 45, lanes 18-30). Indeed, as disclosed at page 43, lanes 12-22, these sequences represent portions of a single *HindIII* fragment containing the entire gene, which was isolated from BAC genomic library and subcloned into pKS plasmid for sequencing. Accordingly, the search and examination of each of the sequence species from SEQ ID NOS: 1-10 and 13-28 would be necessarily co-extensive, and can be made without undue burden on the Examiner.

Furthermore, as specified in MPEP 803.04 (emphasis added): "to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided sua sponte to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See Examination of Patent Applications Containing Nucleotide Sequences, 1192 O.G. 68 (November 19, 1996). It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction."

In light of the foregoing practice, a potential Examiner's requirement to elect a single sequence is traversed. It is believed that the applicants are entitled to election of all sequences comprising SEQ ID NOS: 1-10 and 13-28.

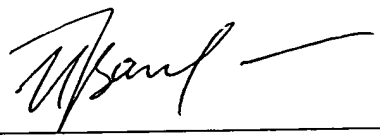
In closing, applicants respectfully submit that the groups of claims designated by the

Examiner fail to define methods and compositions that warrant separate examination and search. The present claims represent a web of knowledge and continuity of effort that merits examination in a single application. Thus, the search and examination of each group is necessarily co-extensive, and in any event would involve such interrelated art that the search and examination of the entire application can be made without undue burden on the Examiner. Accordingly, applicants respectfully request that the Examiner withdraw the Requirement for Restriction and examines all of the pending claims in a single application or at least modifies the Requirement to allow prosecution of more than one of the above groups.

CONCLUSION

Applicants request entry of the foregoing preliminary amendments and remarks in the file history of this application. In view of the above arguments and amendments, withdrawal or modification of the Requirement for Restriction is respectfully requested, and an early action on the merits is courteously solicited.

Respectfully submitted,



Dated April 10, 2001

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PATENT TRADEMARK OFFICE

2427/1E988-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Vincent J. KIDD et al.

Serial No.:	09/477,082	Group Art Unit:	1642
Filed:	December 30, 1999	Examiner:	Jennifer Hunt

For: TUMOR SUPPRESSOR PROTEIN INVOLVED IN DEATH SIGNALING, AND DIAGNOSTICS, THERAPEUTICS, AND SCREENING BASED ON THIS PROTEIN

MARK-UP FOR PRELIMINARY AMENDMENT OF APRIL 10, 2001

Pursuant to 37 C.F.R. §1.121, Applicants provide the following mark-up copy of the amendments requested for the claims in the above-referenced application. This document is submitted simultaneously with an Amendment and Response to the Restriction Requirement mailed March 14, 2001.

CLAIMS:

21. (Amended) A nucleic acid comprising at least a part of the genomic gene encoding CASP8, wherein the nucleic acid is selected from the group consisting of:

a) a *CASP8* genomic DNA;

b) a *CASP8* promoter;

c) a nucleic acid amplified by primers that correspond to a sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, [12,] 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, and 28;

d) a *CASP8* exon;

e) a *CASP8* intron;

f) a nucleic acid having at least 15 bases and hybridizable under stringent conditions to a *CASP8* non-coding sequence.

38. (Amended) A pharmaceutical composition for treating a cancer comprising the vector of claim 3<u>6</u>[2] and a pharmaceutically acceptable carrier.

Respectfully submitted,

Dated April 10, 2001

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